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Clinical Practice Guideline for Systemic Antifungal Prophylaxis in Pediatric Patients With Cancer and Hematopoietic Stem-Cell Transplantation Recipients

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PURPOSE To develop a clinical practice guideline for systemic antifungal prophylaxis in pediatric patients with cancer and hematopoietic stem-cell transplantation (HSCT) recipients.

METHODS Recommendations were developed by an international multidisciplinary panel that included a patient advocate. We conducted a systematic review of systemic antifungal prophylaxis in children and adults with cancer and HSCT recipients. The Grading of Recommendations Assessment, Development, and Evaluation approach was used to make strong or weak recommendations and to classify level of evidence as high, moderate, low, or very low. The panel considered directness of the data to pediatric patients.

RESULTS There were 68 randomized trials included in the systematic review, of which 6 (9%) were conducted in a solely pediatric population. Strong recommendations were made to administer systemic antifungal prophylaxis to children and adolescents receiving treatment of acute myeloid leukemia, to those undergoing allogeneic HSCT pre-engraftment, and to those receiving systemic immunosuppression for graft-versus-host disease treatment. A strong recommendation was made to administer a mold-active agent with an echinocandin or a mold-active azole when systemic antifungal prophylaxis is warranted. For children younger than 13 years of age, an echinocandin, voriconazole, or itraconazole is suggested. Posaconazole may also be used in those age 13 years or older. A strong recommendation against routine administration of amphotericin as systemic antifungal prophylaxis was made.

CONCLUSION We developed a clinical practice guideline for systemic antifungal prophylaxis administration in pediatric patients with cancer and HSCT recipients. Implementation and assessment of guideline-concordant rates and impacts are important future steps.

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Children and adolescents receiving intensive myelo-suppressive chemotherapy and some pediatric hematopoietic stem-cell transplantation (HSCT) recipients are at high risk for invasive fungal disease (IFD) caused by yeasts and molds.¹⁻⁴ In these patients, infections with *Candida* and *Aspergillus* species are most common.¹⁻³ IFDs are important because they are associated with substantial morbidity, delayed cancer treatment, increased health services utilization, and treatment-related mortality.⁵

Systemic antifungal prophylaxis can be an effective approach to reducing IFD. A clinical practice guideline (CPG) facilitates evidence-based clinical care by describing risks and benefits of different management

options based on a systematic review of the literature. Risks and benefits are weighed against each other by a panel of experts to arrive at care recommendations. Previously published CPGs^{6,7} addressing systemic antifungal prophylaxis in pediatric patients are > 5 years old and thus do not consider results of recent trials. In addition, those panels had limited regional and disease representation. Key representatives of two previously published CPGs for pediatric patients (T.L., E.C., L.L.D., A.H.G., E.R., M.S., A.W., P.D.R., and L.S.)^{6,7} were brought together to arrive at a single harmonized CPG, thus improving consistency of recommendations internationally. The objective was to develop a CPG for systemic antifungal prophylaxis in pediatric patients with cancer and HSCT recipients.

CONTEXT

Key Objectives

Which pediatric patients with cancer and hematopoietic stem-cell transplantation (HSCT) recipients should routinely receive systemic antifungal prophylaxis?

Knowledge Generated

Based on a systematic review, an international multidisciplinary guideline panel recommended systemic antifungal prophylaxis be administered to children and adolescents receiving treatment of acute myeloid leukemia, to those undergoing allogeneic HSCT pre-engraftment, and to those receiving systemic immunosuppression for graft-versus-host disease treatment. When systemic antifungal prophylaxis is warranted, an echinocandin or a mold-active azole should be used.

Relevance

This clinical practice guideline for systemic antifungal prophylaxis is important because of the impact of invasive fungal disease in pediatric patients with cancer and HSCT recipients and because of the presence of multiple approaches to invasive fungal disease prophylaxis, including no prophylaxis.

METHODS

Panel Constitution

The panel included representatives from the fields of pediatric hematology/oncology, pediatric HSCT, pediatric infectious diseases, nursing, and pharmacy; a patient advocate; and a CPG methodologist (Data Supplement). Panel members were selected based on clinical and methodologic expertise and geographic representation. All panel members declared potential conflicts of interest, and none precluded participation in this CPG (Data Supplement).

General CPG Development Approach

We used standard approaches to create this CPG,⁸ including the Appraisal of Guidelines for Research and Evaluation II instrument, to direct development.⁹ Financial support for CPG creation was provided by the Pediatric Oncology Group of Ontario. However, CPG development, drafting of recommendations and the manuscript, and the decision to submit for publication were independent from the funder.

The key clinical questions were developed by the panel and are listed in [Table 1](#). The target population is children and adolescents (age 0-18 years) receiving chemotherapy for cancer or undergoing HSCT. Target users are physicians, microbiologists, nurse practitioners, nurses, pharmacists, antibiotic stewards, and other health care professionals who are concerned with infectious complications in pediatric patients receiving chemotherapy or undergoing HSCT.

Panel members identified and rated the importance of outcomes by consensus. Outcomes that were considered critical for decision making were proven or probable IFD, mold infection or yeast infection, fungal infection-related mortality, and overall mortality. Outcomes considered important were drug-related adverse effects and antifungal resistance. Empirical antifungal therapy was not considered

important and, thus, not evaluated. Because changing diagnostic technologies can influence possible IFD events, possible IFD was included post hoc as an outcome.

To rate the level of evidence and to formulate recommendations, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used.¹⁰ The level of evidence indicates the degree of certainty that estimates from the systematic review reflect effects of prophylaxis in our target population, namely pediatric patients with cancer and HSCT recipients. Evidence was rated as high, moderate, low, or very low. Rating was downgraded if there were limitations in study design, lack of consistency, or imprecision or if direct data were lacking. Considering the level of evidence, strong or weak recommendations were made. Strong recommendations were made where benefits clearly outweighed the risks or vice versa and, thus, patients should receive or not receive the intervention as a general policy. Weak recommendations were made where the benefits and risks were closely matched or where there was uncertainty in their estimates. Efficacy, toxicity, and resources, including costs, influenced recommendation formulation.

Searching, Selecting, and Describing the Evidence

The evidence base used to create this CPG was founded on randomized clinical trials because they are generally less susceptible to bias in comparison with observational trials.¹¹ The literature search was performed with the assistance of a library scientist in the following databases: MEDLINE, MEDLINE In-Process, MEDLINE Epub Ahead of Print, and Embase. The Data Supplement shows the full search strategy. Inclusion criteria were fully published randomized trials with a parallel group design that compared the administration of a systemic antifungal agent to any control group as prophylaxis. At least 90% of study participants had to be patients with cancer receiving

TABLE 1. Summary of Recommendations for Systemic Antifungal Prophylaxis in Children and Adolescents With Cancer and Pediatric HSCT Recipients

Health Questions and Recommendations	Strength of Recommendation and Level of Evidence
Which pediatric patients with cancer and HSCT recipients should routinely receive systemic antifungal prophylaxis?	
Acute myeloid leukemia	
1. Administer systemic antifungal prophylaxis to children and adolescents receiving treatment of acute myeloid leukemia that is expected to result in profound and prolonged neutropenia.	Strong recommendation; high-quality evidence
Remarks: This strong recommendation is based on the increasing benefit of systemic antifungal prophylaxis versus no prophylaxis to reduce proven or probable IFD as the risk for IFD increases. Although this recommendation advocates for a universal prophylaxis approach, future research should identify patient and treatment factors that may allow tailoring of prophylaxis to those at the highest risk for IFD.	
Acute lymphoblastic leukemia	
2. Consider administering systemic antifungal prophylaxis to children and adolescents with newly diagnosed and relapsed acute lymphoblastic leukemia at high risk for IFD.	Weak recommendation; low-quality evidence
Remarks: Children and adolescents with acute lymphoblastic leukemia encompass a group with wide variability in IFD risk that is not solely accounted for by relapse status. Those with relapsed acute lymphoblastic leukemia receiving intensive myelosuppressive chemotherapy are most likely to warrant systemic antifungal prophylaxis, whereas greater uncertainty is present for those with newly diagnosed acute lymphoblastic leukemia. Given the heterogeneity in IFD risk across protocols overall and by phase of treatment, adaptation will be required for each protocol to recommend whether and when systemic antifungal prophylaxis should be administered.	
3. Do not routinely administer systemic antifungal prophylaxis to children and adolescents with acute lymphoblastic leukemia at low risk for IFD.	Strong recommendation; low-quality evidence
Remarks: A low risk for IFD can be inferred based on absence of risk factors such as prolonged neutropenia and corticosteroid administration and observed IFD rates across different protocols. This group includes, for example, pediatric patients receiving maintenance chemotherapy for acute lymphoblastic leukemia.	
Other malignancies including most patients with lymphomas and solid tumors	
4. Do not routinely administer systemic antifungal prophylaxis to children and adolescents with cancer at low risk for IFD, such as most pediatric patients with lymphomas and solid tumors.	Strong recommendation; moderate-quality evidence
Remarks: In pediatric patients at low risk for IFD, the benefit of systemic antifungal prophylaxis is likely to be small and outweighed by the risk for adverse effects, costs, and inconvenience. Thus, systemic antifungal prophylaxis should not routinely be administered in this setting.	
HSCT	
5. Administer systemic antifungal prophylaxis to children and adolescents undergoing allogeneic HSCT pre-engraftment and to those receiving systemic immunosuppression for the treatment of graft-versus-host disease.	Strong recommendation; moderate-quality evidence
Remarks: The panel recognized that these two phases of therapy are associated with different epidemiology of IFD. However, the nature of the trials included in the systematic review precluded the ability to make separate recommendations for them. This strong recommendation was influenced by the finding in the systemic prophylaxis versus no systemic prophylaxis stratified analysis that HSCT recipients experienced greater benefit in IFD reduction compared with chemotherapy recipients. In addition, the subgroup analysis showed that among the HSCT stratum, prophylaxis significantly reduced fungal infection–related mortality.	
6. We suggest that systemic antifungal prophylaxis not be used routinely in children and adolescents undergoing autologous HSCT.	Weak recommendation; low-quality evidence
Remarks: This weak recommendation was based on the lower risk for IFD associated with autologous HSCT. There is less certainty in the setting of tandem transplantations where the cumulative duration of neutropenia may be longer.	
If systemic antifungal prophylaxis is planned, which agents should be used?	
7. If systemic antifungal prophylaxis is warranted, administer a mold-active agent.	Strong recommendation; high-quality evidence
(continued on following page)	

TABLE 1. Summary of Recommendations for Systemic Antifungal Prophylaxis in Children and Adolescents With Cancer and Pediatric HSCT Recipients (continued)

Health Questions and Recommendations	Strength of Recommendation and Level of Evidence
Remarks: This strong recommendation was based on the comparison of different systemic antifungal prophylaxis agents where mold-active agent versus fluconazole significantly reduced proven or probable IFD, mold infection, and IA, and reduced fungal infection–related mortality. Direct pediatric data were available, increasing quality of the evidence.	
8. In choosing a mold-active agent, administer an echinocandin or a mold-active azole.	Strong recommendation; moderate-quality evidence
Remarks: The choice of specific mold-active agent is influenced by multiple factors including local epidemiology, adverse effect profile, potential for drug interactions, costs, and jurisdictional availability. For children younger than 13 years of age, an echinocandin, voriconazole, or itraconazole is suggested based on efficacy and adverse effects. In those 13 years of age and older, posaconazole also is an option.	
9. Do not use amphotericin routinely as systemic antifungal prophylaxis.	Strong recommendation; low-quality evidence
Remarks: This strong recommendation was based on the finding that both conventional and lipid formulations of amphotericin were not more effective than fluconazole in reducing IFD. It is important to note that liposomal amphotericin was not included in studies comparing amphotericin versus fluconazole and, thus, there is less certainty about the benefits and risks of this formulation.	
When should systemic antifungal prophylaxis be started and stopped?	
10. If systemic antifungal prophylaxis is warranted, consider administration during periods of observed or expected severe neutropenia. For allogeneic HSCT recipients, consider administration during systemic immunosuppression for graft-versus-host disease treatment.	Weak recommendation; low-quality evidence
Remarks: There are limited data that inform the decision of when to initiate and discontinue systemic antifungal prophylaxis. This recommendation was based on the criteria used in the included randomized trials and the anticipated highest risk period.	

Abbreviations: HSCT, hematopoietic stem-cell transplantation; IA, invasive aspergillosis; IFD, invasive fungal disease.

chemotherapy or HSCT recipients. There was no restriction by language. We excluded studies of ketoconazole because both the US Food and Drug Administration and the European Medicines Agency have warned against its systemic use as a result of the risk for hepatic toxicities, adrenal suppression, and drug interactions.^{12,13} The search included studies published from January 1, 1980, to November 18, 2019.

The primary outcome of the systematic review was proven or probable IFD. Other outcomes were proven or probable mold infection, proven or probable invasive aspergillosis (IA), proven or probable yeast infection, overall mortality, fungal infection–related mortality, and discontinuation of antifungal prophylaxis as a result of an adverse effect. For all IFD outcomes (namely IFD, mold infection, IA, and yeast infection), if the study used the European Organisation for Research and Treatment in Cancer (EORTC)/Mycosis Study Group criteria for categorization, proven or probable IFD outcomes were abstracted. If a study did not use the EORTC criteria, IFD outcomes were mapped to EORTC categories (2008 revised version)¹⁴ by four investigators (T.L., P.P., P.D.R., and L.S.) by consensus where possible. These outcomes were considered missing if mapping was not possible.

We compared systemic antifungal prophylaxis, mold-active prophylaxis, and non–mold-active prophylaxis (fluconazole) versus no systemic prophylaxis, both by group and

then stratified by specific agent evaluated. We next compared different systemic antifungal prophylaxis agents focusing on mold-active agents (amphotericin, mold-active azole, or echinocandin) versus fluconazole as a group and then broken down by subcategories and specific agents. We also compared mold-active azole versus echinocandin.

Study and demographic characteristics were year of publication, country of study conduct, age of participants, cancer diagnosis or HSCT type, and number of randomly assigned participants. Study-level covariates were participant age group (adult, pediatric, or both), treatment group (chemotherapy only, HSCT only, or both chemotherapy and HSCT), and EORTC criteria use to classify IFD (yes or no). Age group was categorized as adult when all participants were older than 15 years of age, and it was categorized as pediatric when all participants were younger than 25 years of age or when the median or mean age was younger than 15 years. Agent dose and schedule, start and stop criteria, and use of therapeutic drug monitoring were also collected. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials was used.¹⁵

Titles and abstracts of articles identified by the systematic review were screened, and articles potentially meeting eligibility criteria were evaluated at full text. All steps, including screening, full text review, and data abstraction, were performed in duplicate (V.F., P.P., or P.D.R.). If

disagreement occurred, it was resolved by consensus or with arbitration by a third reviewer (T.L. or L.S.). Agreement in study inclusion was described using the kappa statistic.¹⁶

Statistical Analysis

Data synthesis used the risk ratio (RR) with the 95% CI to describe prophylaxis effects. In this analysis, $RR < 1$ indicates that the intervention is better than control. The Mantel-Haenszel random effects model in Review Manager 5.3 (Cochrane Collaboration, Nordic Cochrane Centre, London, United Kingdom)¹⁷ was used to estimate treatment effects. Outcomes were synthesized where there were at least three studies for main analysis and where there were at least two studies for each stratum in stratified analysis. If the number of events was zero in both groups, that study was not included in synthesis, which is considered a standard approach in meta-analyses.¹⁵ If a study included more than two randomized groups, the control group weight was proportionately divided between the different intervention groups, and all intervention versus control comparisons were included in the meta-analysis.¹⁵ We also calculated the I^2 value, which is the percentage of total variation across studies as a result of heterogeneity rather than chance.¹⁵

Stratified analysis focused on two comparisons and four outcomes to limit multiple testing. The two comparisons were systemic antifungal prophylaxis versus no systemic antifungal prophylaxis, and mold-active agent versus fluconazole. The four outcomes were proven or probable IFD, proven or probable mold infection, fungal infection–related mortality, and antifungal discontinuation as a result of adverse effect (only for mold-active agent v fluconazole comparison). Strata evaluated were study-level covariates and, in addition, the risk for IFD and mold in the control group (above and below the median value). P value for interaction (P_{int}) was used to determine whether heterogeneity in the prophylaxis effect could be explained by study-level covariates; we did not focus on stratum-specific P values.¹⁵

Funnel plots were used to explore the possibility of publication bias when at least 10 studies were available for an analysis.¹⁵ Funnel plots are graphical displays of the effect measure on the x-axis and precision on the y-axis. An absence of studies in the right lower quadrant (for this specific analysis) may indicate publication bias. If there was a suggestion of publication bias, we used the trim and fill technique to describe its potential impact. In this event, we removed outlying studies (trim) and added hypothetical negative studies with equal weight (fill).¹⁵ Analysis used Review Manager 5.3.¹⁷

Formulating Recommendations, Assigning Quality of Evidence, and Manuscript Preparation

We drafted evidence tables based on the systematic review results. Recommendations were developed during a series of conference calls and an in-person meeting held in Lyon,

France, on October 25, 2019. Deliberations also used the results of a recently published systematic review of risk factors for IFD.⁴ Draft versions of the recommendations and manuscript were circulated until approved by all authors. We used the peer-review mechanism as an efficient approach to external review. We plan to update this CPG in 5 years or sooner in the event of important new information.

RESULTS

The search strategy identified 68 randomized trials that were included in the systematic review. Agreement in study inclusion between reviewers was perfect ($\kappa = 1.00$). The Data Supplement illustrates the flow diagram of study identification, selection, and reasons for exclusion. Health questions, recommendations, strength of recommendation, level of evidence, and remarks are summarized in Table 1. Characteristics of the included trials are listed in Table 2, and study-level details are provided in the Data Supplement. Among the five trials of voriconazole and six trials of posaconazole, none used therapeutic drug monitoring to systematically guide dosing. Six studies were conducted solely in a pediatric population (Data Supplement).

Table 3 provides comparisons between systemic antifungal prophylaxis versus no systemic antifungal prophylaxis for all studies and stratified by mold-active agent and non-mold-active agent (fluconazole). The Data Supplement further stratifies these analyses by agent evaluated, namely amphotericin (all formulations), lipid amphotericin formulations, and itraconazole. Compared with no systemic prophylaxis, systemic antifungal prophylaxis significantly reduced proven or probable IFD ($RR, 0.47$; 95% CI, 0.36 to 0.60; $P < .00001$), proven or probable yeast infection ($RR, 0.31$; 95% CI, 0.22 to 0.44; $P < .00001$), and fungal infection–related mortality ($RR, 0.57$; 95% CI, 0.40 to 0.81; $P = .002$). The effects of mold-active agent and non-mold-active agent versus no systemic antifungal prophylaxis were similar to the overall analysis for the reduction of IFD, yeast infection, and fungal infection–related mortality. The Data Supplement shows stratified analyses of comparisons between systemic antifungal prophylaxis versus no systemic prophylaxis for the outcomes of proven or probable IFD, proven or probable mold infection, and fungal infection–related mortality. For the outcome of proven or probable IFD, significantly greater benefit was observed with increasing risk for IFD in the control group, both when the risk was dichotomized ($P_{int} = .03$; Data Supplement) and when the risk was divided into quartiles ($P_{int} = .0009$; Data Supplement). More specifically, the effect of prophylaxis was an RR of 0.72 (95% CI, 0.43 to 1.20) for those in the lowest quartile (smallest risk for IFD) compared with an RR of 0.25 (95% CI, 0.17 to 0.36) for those in the highest quartile (greatest risk for IFD). Benefit was also significantly greater in patients receiving HSCT only compared with chemotherapy only or chemotherapy plus HSCT ($P_{int} = .03$). The effect of prophylaxis did not differ based

TABLE 2. Characteristics of Studies Included in the Systematic Review

Characteristic and Stratum	No. of Studies (N = 68; %) ^a
Study population characteristics	
Treatment	
Chemotherapy only	25 (37)
Hematopoietic stem-cell transplantation only	25 (37)
Both chemotherapy and stem-cell transplantation	18 (26)
Age of participants	
Adult	41 (60)
Pediatric	6 (9)
Both	20 (29)
Not stated	1 (1)
Interventions included in synthesis	
Any systemic antifungal v no systemic antifungal prophylaxis ^b	27 (40)
Mold-active agent v no systemic antifungal prophylaxis ^b	14 (21)
Non-mold-active agent (fluconazole) v no systemic antifungal prophylaxis ^b	13 (19)
Mold-active agent (amphotericin, echinocandin, or mold-active azole) v fluconazole	21 (31)
Amphotericin (conventional or lipid) v fluconazole	4 (6)
Echinocandin (caspofungin or micafungin) v fluconazole	4 (6)
Mold-active azole (itraconazole, posaconazole, or voriconazole) v fluconazole	13 (19)
Mold-active azole v echinocandin	3 (4)
Risk of bias	
Adequate sequence generation	30 (44)
Adequate allocation concealment	12 (18)
Participants and personnel blinded	10 (15)
Outcome assessors blinded	12 (18)
Lack of attrition bias	64 (94)
Free of selective reporting	61 (90)

^aPercentages may not add to 100% as a result of rounding.

^bNo systemic antifungal prophylaxis consists of placebo, no treatment, or nonsystemic antifungals.

on risk for mold infection in the control group ($P_{int} = .90$). We also performed an analysis of amphotericin (conventional or lipid formulations) versus no systemic antifungal prophylaxis stratified by daily dosing versus nondaily dosing. Effects on IFD and fungal infection-related mortality were similar when comparing daily and nondaily dosing (Data Supplement).

Table 4 summarizes the comparisons of different systemic antifungal prophylaxis groups, with additional comparisons by subcategory and agents shown in the Data Supplement. Use of a mold-active agent (amphotericin [conventional or lipid formulations], echinocandin, or mold-active azole), when compared with fluconazole, significantly reduced proven or probable IFD (RR, 0.61; 95% CI, 0.49 to 0.76; $P < .00001$), proven or probable mold infection (RR, 0.56; 95% CI, 0.42 to 0.74; $P < .0001$), proven or probable IA (RR, 0.44; 95% CI, 0.30 to 0.65; $P < .0001$), and fungal infection-related mortality (RR, 0.64; 95% CI, 0.45 to 0.91; $P = .01$). However, use of a mold-active agent significantly

increased discontinuation of antifungal prophylaxis as a result of an adverse effect (RR, 1.72; 95% CI, 1.09 to 2.71; $P = .02$). When stratified by type of antifungal, amphotericin (conventional or lipid formulations) did not reduce proven or probable IFD (RR, 0.99; 95% CI, 0.52 to 1.88; $P = .98$) but did significantly increase discontinuation of antifungal prophylaxis as a result of an adverse effect (RR, 5.63; 95% CI, 1.17 to 27.02; $P = .03$). In contrast, the benefits of echinocandin versus fluconazole and mold-active azole versus fluconazole in reducing proven or probable IFD, proven or probable mold infection, and proven or probable IA were similar to the overall comparison of mold-active agent versus fluconazole. Table 4 also shows that mold-active azole, when compared with echinocandin, did not have a statistically significant different effect on IFD, mold infection, IA, or yeast infection, but did significantly increase discontinuation of antifungal prophylaxis as a result of an adverse effect. The Data Supplement shows stratified analyses of

TABLE 3. Systemic Antifungal Prophylaxis Versus No Systemic Antifungal Prophylaxis

Comparison and Outcome	No. of Studies	RR	95% CI	I ² (%)	P
Any systemic antifungal v no systemic antifungal prophylaxis ^a					
Proven or probable IFD	27	0.47	0.36 to 0.60	15	< .00001
Proven or probable mold infection	24	0.80	0.48 to 1.33	21	.39
Proven or probable IA	24	0.87	0.50 to 1.52	21	.63
Proven or probable yeast infection	24	0.31	0.22 to 0.44	0	< .00001
Overall mortality	25	0.85	0.73 to 1.00	10	.05
Fungal infection–related mortality	19	0.57	0.40 to 0.81	0	.002
Mold-active agent (amphotericin [conventional or lipid], echinocandin, or mold-active azole) v no systemic antifungal prophylaxis					
Proven or probable IFD	14	0.50	0.35 to 0.72	8	.0002
Proven or probable mold infection	12	0.52	0.22 to 1.26	34	.15
Proven or probable IA	12	0.60	0.23 to 1.55	39	.29
Proven or probable yeast infection	12	0.37	0.21 to 0.65	0	.0007
Overall mortality	14	0.86	0.69 to 1.08	0	.19
Fungal infection–related mortality	11	0.64	0.38 to 1.10	0	.11
Non-mold-active agent (fluconazole) v no systemic prophylaxis					
Proven or probable IFD	13	0.44	0.31 to 0.63	26	< .00001
Proven or probable mold infection	12	1.13	0.63 to 2.04	0	.68
Proven or probable IA	12	1.28	0.66 to 2.49	0	.47
Proven or probable yeast infection	12	0.28	0.18 to 0.44	0	< .00001
Overall mortality	11	0.84	0.65 to 1.07	29	.16
Fungal infection–related mortality	8	0.50	0.29 to 0.86	9	.01

Abbreviations: IA, invasive aspergillosis; IFD, invasive fungal disease; RR, risk ratio.

^aNo systemic antifungal prophylaxis consists of placebo, no treatment, or nonsystemic antifungals.

mold-active agent versus fluconazole; no significant interactions were observed.

The Data Supplement shows systemic antifungal prophylaxis initiation and discontinuation criteria by diagnosis or treatment group and also illustrates sensitivity analyses where publication bias was suggested in funnel plots. None substantially altered interpretation of the base analyses. In addition, the Data Supplement shows synthesis in which possible IFD, mold, or IA was reported. These did not substantially alter interpretation of the base analysis. Research gaps are outlined in Table 5.

Recommendation 1

Administer systemic antifungal prophylaxis to children and adolescents receiving treatment of acute myeloid leukemia that is expected to result in profound and prolonged neutropenia (Evidence quality: high; Strength of recommendation: strong).

Explanation. This recommendation was informed by the systematic review of risk factors identifying that patients with acute myeloid leukemia are at high risk for IFD. The benefit of systemic antifungal prophylaxis was greater for those at higher risk for proven or probable IFD, leading to this strong recommendation.

Recommendation 2

Consider administering systemic antifungal prophylaxis to children and adolescents with newly diagnosed and relapsed acute lymphoblastic leukemia at high risk for IFD (Evidence quality: low; Strength of recommendation: weak).

Explanation. The risk for IFD in pediatric acute lymphoblastic leukemia is protocol and phase specific. This risk is also dependent on remission status; chemotherapy-related neutropenia; and corticosteroid formulation, dose, and duration of administration. On the basis of the systematic review of risk factors for IFD,⁴ the panel believed that there are likely to be subgroups of pediatric patients with acute lymphoblastic leukemia who would benefit from systemic antifungal prophylaxis. However, the panel was unable to identify comprehensive baseline data on IFD incidence in the various acute lymphoblastic leukemia populations that would permit more specific recommendations. The panel also acknowledged that treatments for poor-risk acute lymphoblastic leukemia are changing. For example, immunotherapies are being used increasingly and may be associated with a lower risk for IFD compared with conventional, myelosuppressive chemotherapy. Given these factors, the panel did not

TABLE 4. Comparison of Different Systemic Antifungal Prophylaxis Agents

Comparison and Outcome	No. of Studies	RR	95% CI	I ² (%)	P
Mold-active agent (amphotericin [conventional or lipid], echinocandin or mold-active azole) v fluconazole					
Proven or probable IFD	21	0.61	0.49 to 0.76	0	< .00001
Proven or probable mold infection	19	0.56	0.42 to 0.74	0	< .0001
Proven or probable IA	18	0.44	0.30 to 0.65	0	< .0001
Proven or probable yeast infection	17	1.10	0.71 to 1.70	0	.68
Overall mortality	16	1.01	0.88 to 1.17	0	.87
Fungal infection–related mortality	14	0.64	0.45 to 0.91	0	.01
Discontinuation of antifungal as a result of AE	18	1.72	1.09 to 2.71	79	.02
Amphotericin (conventional or lipid) v fluconazole					
Proven or probable IFD	4	0.99	0.52 to 1.88	0	.98
Proven or probable mold infection	3 ^a				
Proven or probable IA	4	1.18	0.28 to 4.97	0	.82
Proven or probable yeast infection	3 ^a				
Overall mortality	4	1.16	0.81 to 1.67	0	.41
Fungal infection–related mortality	3	0.91	0.39 to 2.16	0	.83
Discontinuation of antifungal as a result of AE	4	5.63	1.17 to 27.02	57	.03
Echinocandin (caspofungin or micafungin) v fluconazole					
Proven or probable IFD	4	0.61	0.36 to 1.03	0	.06
Proven or probable mold infection	4	0.59	0.31 to 1.09	0	.09
Proven or probable IA	3	0.17	0.04 to 0.66	0	.01
Proven or probable yeast infection	3	1.08	0.31 to 3.76	18	.91
Overall mortality	4	0.77	0.51 to 1.17	0	.22
Fungal infection–related mortality	3	0.49	0.14 to 1.73	0	.27
Discontinuation of antifungal as a result of AE	4 ^a				
Mold-active azole (itraconazole, voriconazole, or posaconazole) v fluconazole					
Proven or probable IFD	13	0.56	0.42 to 0.75	11	< .0001
Proven or probable mold infection	12	0.55	0.40 to 0.75	0	.0002
Proven or probable IA	11	0.45	0.29 to 0.70	10	.0004
Proven or probable yeast infection	11	0.85	0.48 to 1.53	0	.59
Overall mortality	8	1.02	0.84 to 1.23	15	.88
Fungal infection–related mortality	8	0.62	0.37 to 1.04	32	.07
Discontinuation of antifungal as a result of AE	10	1.73	1.04 to 2.88	82	.04
Mold-active azole v echinocandin					
Proven or probable IFD	3	0.73	0.32 to 1.65	0	.45
Proven or probable mold infection	3	0.74	0.21 to 2.62	0	.65
Proven or probable IA	3	0.88	0.24 to 3.21	0	.85
Proven or probable yeast infection	3	0.83	0.30 to 2.27	0	.71
Overall mortality	3	0.83	0.28 to 2.46	29	.73
Discontinuation of antifungal as a result of AE	3	11.04	1.28 to 95.40	74	.03

Abbreviations: AE, adverse effects; IA, invasive aspergillosis; IFD, invasive fungal disease; RR, risk ratio.

^aNo synthesis possible because there were less than three studies with an event in at least one arm.

make a strong recommendation for antifungal prophylaxis in pediatric patients with acute lymphoblastic leukemia. Rather, the panel made a weak recommendation with the

understanding that protocol-specific recommendations adjusted to specific phases of therapy such as induction or reinduction are required.

Recommendation 3

Do not routinely administer systemic antifungal prophylaxis to children and adolescents with acute lymphoblastic leukemia at low risk for IFD (Evidence quality: low; Strength of recommendation: strong).

Explanation. For children and adolescents with acute lymphoblastic leukemia, a low risk for IFD can be inferred based on absence of risk factors such as prolonged neutropenia and corticosteroid administration, combined with observed IFD rates across different protocols and phases of therapy. This group includes, for example, pediatric patients receiving maintenance chemotherapy for acute lymphoblastic leukemia.

Recommendation 4

Do not routinely administer systemic antifungal prophylaxis to children and adolescents with cancer at low risk for IFD, such as most pediatric patients with lymphomas and solid tumors (Evidence quality: moderate; Strength of recommendation: strong).

Explanation. In pediatric patients at low risk for IFD, benefit of systemic antifungal prophylaxis is likely to be small and outweighed by the risk for adverse effects, costs, and inconvenience. Thus, systemic antifungal prophylaxis should not routinely be administered in this setting. It is important to emphasize that some patients with lymphomas and solid tumors are at high risk for IFD, such as those with advanced Burkitt lymphoma and some infants with brain tumors. Thus, implementation must consider patient- and treatment-specific risk factors rather than relying on diagnosis alone in deciding which populations merit antifungal prophylaxis.

Recommendation 5

Administer systemic antifungal prophylaxis to children and adolescents undergoing allogeneic HSCT pre-engraftment and to those receiving systemic immunosuppression for the treatment of graft-versus-host disease (GVHD; Evidence quality: moderate; Strength of recommendation: strong).

Explanation. The panel recognized that pre-engraftment and during systemic immunosuppression for the treatment of GVHD were two distinct periods, each increasing the risk for IFD but with different epidemiology. The Data Supplement shows that many studies of allogeneic HSCT recipients included both periods, with few studies focusing on the period of immunosuppression for GVHD treatment. Thus, the panel felt this lack of granularity precluded separate recommendations for these two different periods.

This strong recommendation was influenced by the finding in the systemic prophylaxis versus no systemic prophylaxis stratified analysis that HSCT recipients experienced greater benefit in proven or probable IFD reduction compared with chemotherapy recipients (Data Supplement). In addition, the subgroup analysis showed that among the HSCT stratum, antifungal prophylaxis significantly reduced fungal infection-related mortality (Data Supplement). Although the adult data were clearer, these data may be less generalizable to pediatric patients because of different transplantation approaches such as stem-cell source. As a result, the evidence quality was reduced. The panel suggested that administration in patients receiving systemic treatment of GVHD was reasonable based on risk factors for IFD but could not provide more granularity around whether there is a subgroup in which GVHD treatment is sufficiently short as to not warrant antifungal prophylaxis.

TABLE 5. Key Knowledge Gaps Related to Systemic Antifungal Prophylaxis Among Children and Adolescents With Cancer and Pediatric Hematopoietic Stem-Cell Transplantation Recipients

Knowledge Gap

Identifying personalized risk factors for IFD, allowing for more targeted prophylaxis among patients at highest risk for IFD
Describing the risk for IFD with recently developed modalities of cancer therapy including immunotherapy
Determining whether fluconazole prophylaxis combined with sensitive diagnostic tests and procedures to detect IFD is as effective as prophylaxis with mold-active agents
Describing the risks and benefits of lipid formulations of amphotericin prophylaxis compared with other mold-active agent prophylaxis
Identifying optimal systemic antifungal prophylaxis for infants and neonates
Determining ideal dosing and scheduling of systemic antifungal prophylaxis agents
Determining whether therapeutic drug monitoring has a role in guiding mold-active azole dosing when administered for prophylaxis
In an era of mold-active prophylaxis, evaluating the comparative effectiveness of different diagnostic and therapeutic antifungal approaches including preemptive and empirical treatment
Determining how to best develop and implement a fungal surveillance program
Evaluating antifungal resistance after implementation of different prophylactic antifungal strategies
Understanding how to adapt this clinical practice guideline for low- and middle-income country settings
Understanding the contribution of environmental interventions such as high-efficiency particulate air filtration to the prevention of IFD
Assessing clinical practice guideline concordance in routine clinical care and impact of concordant v nonconcordant practices

Abbreviation: IFD, invasive fungal disease.

Recommendation 6

We suggest that systemic antifungal prophylaxis not be used routinely in children and adolescents undergoing autologous HSCT (Evidence quality: low; Strength of recommendation: weak).

Explanation. A lower risk for IFD associated with autologous HSCT can be inferred from the systematic review of IFD risk factors.⁴ Consequently, systemic antifungal prophylaxis was not recommended for this group. However, there was less certainty in the setting of tandem transplantations where the cumulative duration of neutropenia may be longer. The degree of mucositis associated with specific conditioning regimens may also influence IFD risk and may affect the decision to administer antifungal prophylaxis.

Recommendation 7

If systemic antifungal prophylaxis is warranted, administer a mold-active agent (Evidence quality: high; Strength of recommendation: strong).

Explanation. This strong recommendation was based on the comparison of different systemic antifungal prophylaxis agents (Table 4) where a mold-active agent versus fluconazole significantly reduced proven or probable IFD, mold infection, and IA, and reduced fungal infection–related mortality. Although a mold-active agent also increased adverse effects, the panel felt the benefits outweighed the negative aspects. Direct pediatric data were available, increasing quality of the evidence.

Trials comparing a mold-active agent versus fluconazole were presumably conducted in settings where there is an appreciable risk for mold infection. In settings where the risk for mold is sufficiently low, fluconazole may be an appropriate choice for prophylaxis.

Recommendation 8

In choosing a mold-active agent, administer an echinocandin or a mold-active azole (Evidence quality: moderate; Strength of recommendation: strong).

Explanation. If systemic antifungal prophylaxis is warranted, the choice of which specific mold-active agent is influenced by multiple factors including local epidemiology, adverse effect profile, drug interaction potential, costs, and jurisdictional availability. All mold-active agents have disadvantages. For example, echinocandins must be administered intravenously daily, which may make this option less desirable for ambulatory populations. Use of mold-active azoles may be limited by drug interactions, hepatotoxicity, and adverse effects resulting in discontinuation of prophylaxis. For children younger than 13 years of age, an echinocandin, voriconazole, or itraconazole is suggested based on efficacy, adverse effects, and availability of pediatric dosing information. In settings where all agents are available, either an echinocandin or voriconazole is favored based on toxicity profile. However, itraconazole may be

used if other options are not available. Posaconazole may also be used in those 13 years of age and older. When using mold-active azoles, best practices with respect to therapeutic drug monitoring should be applied.

Recommendation 9

Do not use amphotericin routinely as systemic antifungal prophylaxis (Evidence quality: low; Strength of recommendation: strong).

Explanation. This strong recommendation was based on the finding that amphotericin was not more effective than fluconazole in reducing proven or probable IFD but was associated with more adverse effects (Table 4). Stratified analysis did not reveal differential efficacy based on whether amphotericin was administered on a daily or nondaily schedule (Data Supplement).

Recommendation 10

If systemic antifungal prophylaxis is warranted, consider administration during periods of observed or expected severe neutropenia. For allogeneic HSCT recipients, consider administration during systemic immunosuppression for GVHD treatment (Evidence quality: low; Strength of recommendation: weak).

Explanation. There are limited data that inform the decision of when to initiate and discontinue systemic antifungal prophylaxis. This recommendation was based both on criteria used in the included randomized trials and the anticipated highest risk periods.

DISCUSSION

This CPG of systemic antifungal prophylaxis is important because of the impact of IFD in pediatric patients with cancer and HSCT recipients and uncertainty in the ideal approach. If systemic antifungal prophylaxis is warranted, the panel made a strong recommendation to administer a mold-active agent with an echinocandin or a mold-active azole. In choosing a specific agent, local epidemiology, adverse effect profile, potential for drug interactions, costs, and jurisdictional availability must be weighed against each other for specific settings. If all agents are available and appropriate from a microbiologic perspective, echinocandins may be favored when limiting adverse effects and hepatotoxicity are valued. Conversely, mold-active azoles may be favored when oral administration and convenience are favored.

It is possible that more broad-spectrum antifungal prophylaxis will change the choice of empirical antifungal therapy, and if the new choice has more adverse effects, the strategy could result in more toxicity overall. Future comparative effectiveness studies should evaluate the overall impact of antifungal prophylaxis selection on empirical antifungal choice and overall toxicities.

We found that fluconazole, when compared with no systemic antifungal prophylaxis, was associated with a reduction in

fungal infection–related mortality but not overall mortality. It is possible that the reduction in fungal infection–related mortality occurred because these trials were conducted at a time when there were fewer IFD treatment options. It is also possible that this reduction is related to classification bias given the challenges in assigning cause of death.⁵

As with all CPGs, a structured approach to local adaptation, implementation, and evaluation is a key consideration. Important factors in this process include a baseline understanding of local and disease-specific epidemiology, establishing a leadership team that will oversee the process, and appropriate engagement and education of key

stakeholders. Pediatric acute lymphoblastic leukemia is a particularly challenging population in which to make universal recommendations regarding systemic antifungal prophylaxis because of the wide variability in treatment regimens, each with differing IFD risk patterns and limitations to specific antifungal agents. Implementation of this CPG will likely require protocol-specific recommendations for patients with acute lymphoblastic leukemia.

In summary, we created a CPG for systemic antifungal prophylaxis in pediatric patients with cancer and HSCT recipients. Implementation and assessment of guideline-concordant rates and impacts are important future steps.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Clinical Practice Guideline for Systemic Antifungal Prophylaxis in Pediatric Patients With Cancer and Hematopoietic Stem-Cell Transplantation Recipients**

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